

# Effect of Polymers on Crystallization in Glass-Forming Molecular Liquids: Equal Suppression of Nucleation and Growth and Master Curve for Prediction

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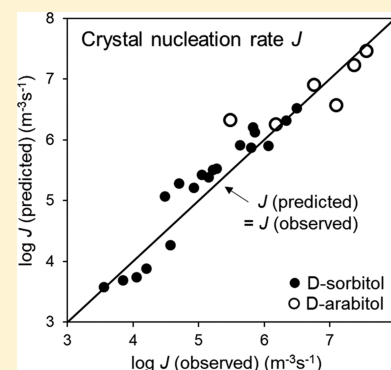
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## Supporting Information

**ABSTRACT:** Crystal nucleation plays a critical role in the stability of supercooled liquids and glasses and is often controlled through addition of polymers. A dissolved polymer alters both the thermodynamics and the kinetics of nucleation, but the current understanding of these effects is limited. The rate of crystal nucleation has been measured in two molecular liquids, D-sorbitol and D-arabitol, containing polyvinylpyrrolidone (PVP) at different concentrations (0–15 wt %) and molecular weights (224 g/mol for the dimer up to 2 Mg/mol). We observe a significant inhibitory effect of PVP on crystal nucleation. Near the peak temperature for the nucleation rate (~20 K above the glass transition temperature), 10 wt % PVP can slow down nucleation by approximately 1 order of magnitude, and the effect increases with polymer concentration exponentially and with molecular weight. Remarkably, the polymer effect on the nucleation rate is nearly the same as that on the crystal growth rate so that the ratio of the two rates is nearly constant at a given temperature independent of polymer concentration and molecular weight. This “master curve” behavior can be used to predict nucleation rates in multicomponent systems from more easily measured growth rates. It argues that nucleation and growth in these viscous liquids are both mobility-limited and that a polymer solute functions mainly as a mobility modifier, suppressing nucleation and growth to a similar degree.



## INTRODUCTION

Glasses are important materials that combine the spatial uniformity of liquids and the mechanical strength of crystals, with applications in numerous technologies. If crystallization is prevented, a liquid under cooling eventually solidifies to a glass. A glass inherits the spatial uniformity of its precursor liquid, useful as windows and optics. A glass can more easily incorporate multiple chemical components than a crystal, providing compositional flexibility in materials design. A glass can be shaped, extruded, and drawn into fibers in the molten state. Pharmaceutical scientists take advantage of the higher solubility of glasses over crystals to deliver poorly soluble drugs.

Crystallization plays an important role in glass science. The very existence of glasses requires avoidance of crystallization, and crystallization during storage can compromise the performance of amorphous materials. On the other hand, controlled crystallization can be exploited to produce glass ceramics—materials with crystallized domains embedded in a glassy matrix, offering useful properties such as ultralow thermal expansion.

Crystallization consists of nucleation and growth, and each step has its own unique kinetics. At present, the growth process in glass-forming liquids is better understood than the nucleation process. Crystal growth rates have been measured in many systems, enabling mining of systematic trends for prediction;<sup>1,2</sup> new mechanisms of crystal growth have been identified that are active in the glassy state, but absent in the fluid state.<sup>3,4</sup> In contrast, the literature is scant on quantitative nucleation rates,<sup>5–9</sup> especially for organic glasses, preventing a systematic analysis. It is difficult at present to make an order-of-magnitude prediction of nucleation rates on theoretical or empirical grounds, while such predictions are becoming realistic for crystal growth.<sup>1,2</sup>

Amorphous materials are often fabricated to contain multiple components in a single phase, and for these systems, a central question is how the additional components influence the crystallization process. Amorphous pharmaceuticals are

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usually formulated with polymers to improve stability and dissolution,<sup>10–12</sup> prompting extensive research on the polymer effect on drug crystallization.<sup>13–17</sup> Here, again, the polymer effect is better understood on crystal growth than on nucleation. It has been shown that even at a low concentration of 1 wt %, a polymer can strongly influence the rate of crystal growth, from a 10-fold increase to a 10-fold decrease, depending on the polymer's segmental mobility relative to the host molecules.<sup>18–20</sup> In contrast to this detailed understanding, comparable progress is yet to be made on crystal nucleation.

The goal of this work is to study the effect of a polymer solute on crystal nucleation in glass-forming molecular liquids. The rate of nucleation has been measured in D-sorbitol and D-arabitol containing polyvinylpyrrolidone (PVP). At present, these two polyalcohols are the only molecular glass-formers for which quantitative nucleation rates are reported.<sup>9</sup> PVP is a commonly used pharmaceutical polymer that is melt-miscible with the two host materials. We observe a significant inhibitory effect of PVP on crystal nucleation. Near the peak temperature for nucleation rate ( $\sim 20$  K above the glass transition temperature  $T_g$ ), 10 wt % PVP can slow crystal nucleation by approximately 1 order of magnitude, and the effect increases with polymer concentration and molecular weight. Interestingly, the polymer has very similar effects on the nucleation rate and the growth rate so that the ratio of the two rates is nearly constant at a given temperature, independent of polymer concentration and molecular weight. This argues that in these viscous liquids, crystal nucleation and growth are both mobility-limited, and the polymer solute acts mainly as a mobility modifier, suppressing nucleation and growth to a similar extent. Our finding is relevant for the selection of polymers for amorphous formulations and the prediction of their performance.

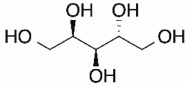
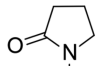
## EXPERIMENTAL SECTION

**Materials.** D-Sorbitol and D-arabitol (both  $\geq 99\%$  pure) were purchased from Sigma-Aldrich. The dimer of vinylpyrrolidone ("VP dimer") was obtained from AbbVie Inc. Polyvinylpyrrolidone (PVP) of different molecular weights was purchased from commercial sources: PVP K12 (Kollidon 12PF) and PVP K30 (Kollidon 30) from BASF; PVP K15 from ISP Technologies; PVP K90 from GAF Chemicals. All the materials were used as received. Table 1 shows the molecular structures of the materials and some of their physical properties.

**Sample Preparation.** PVP was dissolved in a host material by cryomilling (SPEX CertiPrep 6750 with liquid nitrogen as coolant) followed by melting. One gram of D-sorbitol or D-arabitol containing 10 or 15 wt % PVP was cryomilled, and the resulting mixture was diluted by further cryomilling as needed. Cryomilling was performed at 10 Hz for five 2 min cycles, each followed by a 2 min cool down. Before its crystallization was measured, a sample was held in the molten state (12 h at 413 K for D-sorbitol/PVP, 6 h at 403 K for D-arabitol/PVP) to remove air bubbles. A coverslip was then placed over the melt to produce a sandwiched liquid film  $\sim 40$   $\mu\text{m}$  thick. The film thickness was confirmed not to affect the observed rate of nucleation (see below).

**Nucleation Rate.** To measure nucleation rates, each film sample was stored in a desiccator at a chosen temperature maintained within  $\pm 1$  K by different devices: 288 and 278 K using commercial refrigerators, 273 K using the coolant chamber of a circulating cooler, 295 K using an air-conditioned room, and higher temperatures using custom-built mini-ovens. Crystals were observed and counted through a polarized light microscope (Olympus BX53) equipped with a digital camera. The calculation of nucleation rate is described in the Results.

**Table 1. Molecular Structures and Properties of the Materials Used**

	Molecular structure	$M_w$ (g/mol)	$T_g$ (K)
D-sorbitol		182.2	269
D-arabitol		152.1	260
VP dimer		224	217
PVP K12		2000–3000	375
PVP K15		8000	393
PVP K30	$[-\text{CH}_2-\text{CH}-]_n$	44–54 K	437
PVP K90		1–2 M	449

**Crystal Growth Rate.** Crystal growth rate was measured by tracking the advance of a growth front over time; each reported rate was the average of 9–12 measurements in three separate samples. The measurement time intervals were chosen so that the total advance distance of the growth front was at least 30  $\mu\text{m}$ , and there were at least three equally spaced time points to evaluate the constancy of growth rates (see Figure S3 for an example). Crystal growth rates were found to be constant over time.

**Differential Scanning Calorimetry (DSC).** DSC was performed with a TA Q2000 differential scanning calorimeter under 50 mL/min  $\text{N}_2$  purge. Each sample was 5–10 mg placed in a crimped aluminum pan. The glass transition temperature  $T_g$  was measured during heating at 10 K/min after cooling at 10 K/min, and the onset temperature is reported. Melting-point depression by PVP was evaluated by heating at 1 K/min and monitoring the change of the melting end point.

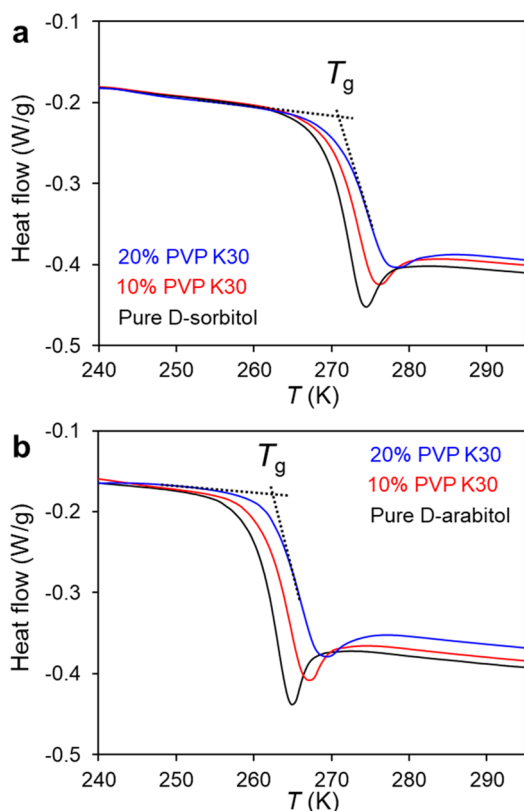
## RESULTS

**Polymer–Host Miscibility.** To interpret a polymer's effect on crystallization, it is necessary to determine whether the polymer is dissolved in or phase separated from the host material. For this purpose, the glass transition temperature  $T_g$  was measured as a function of polymer concentration. Given the higher  $T_g$  of PVP than the host material (Table 1), miscibility implies an increase of  $T_g$  with PVP concentration. This is indeed the case, as illustrated in Figure 1 for PVP K30. In this test, the range of polymer concentration was 0–20 wt %, encompassing the 0–15 wt % range for the crystallization studies and ensuring miscibility in all our experiments. In addition, the  $T_g$  of a polymer-doped material is unchanged during prolonged annealing at nucleation temperatures (see Figure S2 for an example), indicating no phase separation. The miscibility of PVP with the two polyalcohols of this study is consistent with its miscibility with D-mannitol, a stereoisomer of D-sorbitol.<sup>21</sup>

**D-sorbitol/PVP.** Figure 2 shows the typical data collected for measuring the rate of nucleation in D-sorbitol/PVP using the "one-stage" method.<sup>9</sup> In this method, a supercooled liquid is allowed to crystallize for some time  $t_0$  at which individual crystals are observable (Figure 2a). The birth time  $t$  of each crystal is calculated from its current size (radius  $r$ ) and its growth rate ( $u$ ):

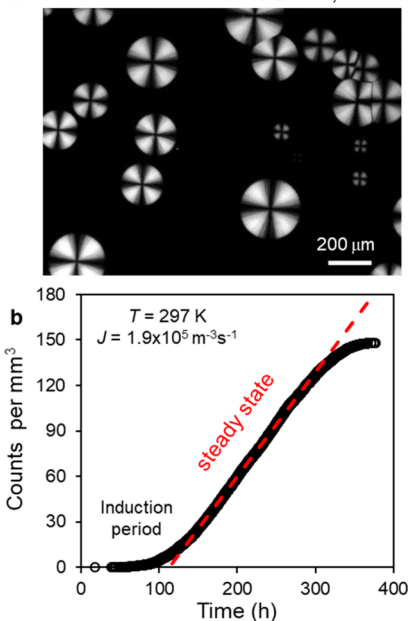
$$t = t_0 - r/u \quad (1)$$

From the birth time of each crystal, the number of nucleation events per unit volume can be obtained as a function of time (Figure 2b). Following an induction period, a



**Figure 1.** DSC heating traces of the glass transition in (a) D-sorbitol/PVP K30 and (b) D-arabitol/PVP K30. Each glass was prepared by cooling at 10 K/min and the subsequent heating scan at 10 K/min is shown. The increase of  $T_g$  with PVP concentration indicates miscibility of components.

**a** 10% PVP K30/D-sorbitol: 297 K, 16.5 d

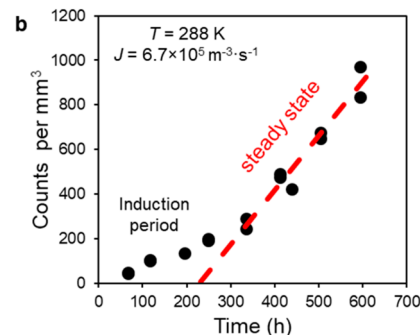
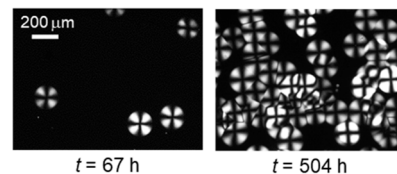


**Figure 2.** One-stage method for measuring crystal nucleation rate in D-sorbitol/PVP. (a) A sample of D-sorbitol containing 10 wt % PVP K30 after 16.5 days at 297 K. A range of crystal size is seen, from which the birth time of each crystal can be calculated (eq 1). (b) Density of crystal nuclei vs time. The slope of this plot at the steady state is the nucleation rate  $J$ .

steady state is reached where nuclei appear at a constant rate. The steady-state nucleation rate  $J$  is the slope indicated in Figure 2b. After the steady-state period, nucleation rate is seen to decrease, which is caused by the reduction of liquid volume available for nucleation.

The one-stage method above is useful when crystal growth is relatively fast but not otherwise. In the latter case, a “two-stage” method<sup>22</sup> was used, and Figure 3 shows the typical result for D-

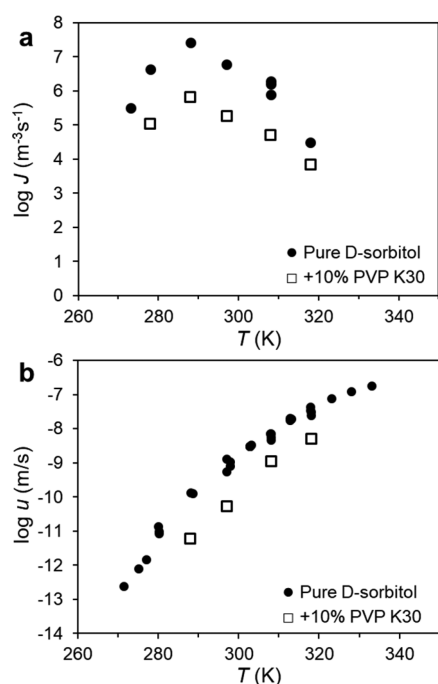
**a** 10% PVP K30/D-sorbitol:  
t at 288 K + 5 h at 313 K



**Figure 3.** Two-stage method for measuring crystal nucleation rates in D-sorbitol/PVP. (a) Crystals observed after D-sorbitol containing 10 wt % PVP K30 spent 67 or 504 h at 288 K followed by 5 h at 313 K. More crystals are observed after a longer time at 288 K. (b) Crystal density vs nucleation time at 288 K. The slope of this plot at the steady state is the nucleation rate  $J$ .

sorbitol/PVP. In this method, a supercooled liquid is nucleated at a low temperature without visible growth and then heated to a high temperature to allow growth of the nuclei to visible size to be counted. The growth temperature is so chosen that nuclei formed at the low temperature can grow quickly, but no new nuclei appear during the time of growth. In the example shown, D-sorbitol containing 10 wt % PVP K30 spent different times at 288 K but the same time (5 h) at 313 K. The sample that spent a longer time at 288 K nucleated more crystals than the sample that spent shorter time. Note that after development, both samples contained crystals of similar size, indicating the crystals were indeed nucleated at the low temperature without significant growth. This latter conclusion has further support from the fact that no crystals were observed at 313 K up to 10 h if the sample was not previously stored at 288 K. Figure 3b shows the density of nuclei developed at 288 K as a function of nucleation time. As in Figure 2b, an induction period is seen in Figure 3b, followed by a steady state of nuclei production; the nucleation rate  $J$  corresponds to the slope of the plot in the steady state.

Figure 4a compares the rates of nucleation  $J$  in pure D-sorbitol<sup>9</sup> and D-sorbitol containing 10 wt % PVP. For clarity, the results are shown only for PVP K30; the results on other PVP molecular weights are collected in Table 2. In the pure liquid,  $J$  reaches a maximum near 290 K ( $T_{max}$ ), and all our measurement of the polymer effect was near that temperature. At all the temperatures investigated, PVP decreases the



**Figure 4.** Effect of 10 wt % PVP K30 on the rate of nucleation (a) and growth (b) in D-sorbitol.

**Table 2.** Effects of PVP on the Rates of Nucleation and Growth in D-Sorbitol<sup>a</sup>

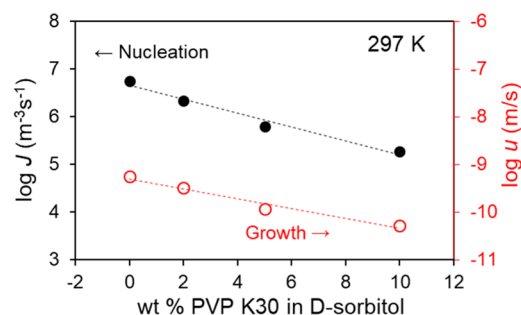
polymer (concentration)	T (K)	log <i>u</i> (m/s)	log <i>J</i> (m <sup>-3</sup> s <sup>-1</sup> )	log <i>J/u</i> (m <sup>-4</sup> )
none (pure D-sorbitol) <sup>b</sup>	273	-12.3	5.5	17.8
	278	-11.4	6.6	18.1
	288	-10.0	7.4	17.4
	297	-9.0	6.8	15.8
	308	-8.1	6.1	14.3
VP dimer (10 wt %)	318	-7.5	4.5	12.0
	297	-9.3	6.5	15.8
	308	-8.3	6.1	14.4
PVP K12 (10 wt %)	318	-7.7	4.6	12.3
	297	-9.7	5.9	15.5
	308	-8.7	5.2	14.0
PVP K15 (10 wt %)	318	-8.1	4.2	12.3
	297	-9.9	5.6	15.5
	308	-8.9	5.1	14.0
PVP K30 (2 wt %)	318	-8.2	4.0	12.3
PVP K30 (5 wt %)	297	-9.5	6.3	15.8
PVP K30 (10 wt %)	297	-9.9	5.8	15.7
	278	-12.6 <sup>c</sup>	5.0	17.7
	288	-11.2	5.8	17.0
	297	-10.3	5.3	15.5
PVP K90 (10 wt %)	308	-9.0	4.7	13.7
	318	-8.3	3.8	12.1
	297	-10.6	4.9	15.5
	308	-9.2	4.5	13.7
	318	-8.4	3.6	12.0

<sup>a</sup>Notes: The error is  $\pm 0.2$  for each reported value of log *u* or log *J*.

<sup>b</sup>The log *u* values for pure D-sorbitol are obtained from a polynomial fit ( $n = 3$ ) of the data in Figure 4b. <sup>c</sup>Obtained by extrapolation of the data in Figure 4b to lower temperature.

nucleation rate, by an average factor of 30 for the sample shown. It is worth noting that the effect of PVP on crystal nucleation (Figure 4a) is similar to that on crystal growth (Figure 4b), despite the different temperature dependence of the two processes.

Figure 5 shows the effects of PVP concentration on the nucleation rate *J* and the growth rate *u* in D-sorbitol at 297 K.



**Figure 5.** Effect of PVP K30 concentration on the rates of crystal nucleation *J* and growth *u* in D-sorbitol at 297 K.

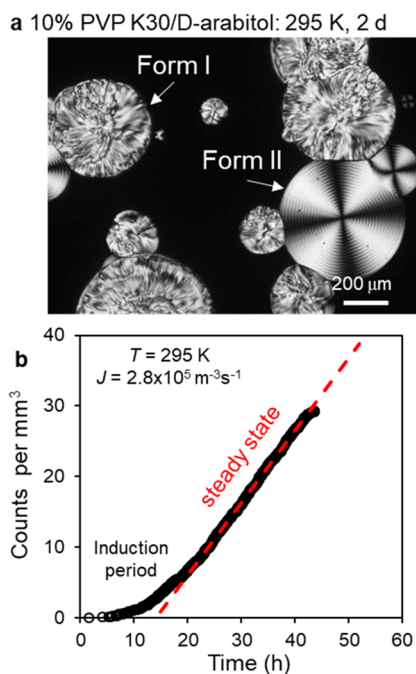
For this comparison, the PVP molecular weight grade was fixed at K30. As the polymer concentration increases, both *J* and *u* decrease and do so at similar rates. To a good approximation, both nucleation and growth rates decrease exponentially with the polymer concentration; that is, the log (rate) versus concentration plot is approximately linear.

In addition to PVP K30, other PVP molecular-weight grades were studied to assess the effect of polymer molecular weight on crystallization in D-sorbitol. These results are found in Table 2. Altogether, the PVP molecular weights cover the range 224 g/mol (VP dimer) to 2 Mg/mol (K90). For each PVP grade tested, we observe qualitatively similar effect as described for PVP K30 (Figures 4 and 5), but the magnitude of the effect increases with increasing molecular weight. This is seen by comparing the entries in Table 2 for different PVP molecular weights at the same concentration (10 wt %) and temperature. In general, the higher the molecular weight, the stronger the polymer's inhibitory effect on nucleation and growth. Furthermore, as we discuss below, the quantitative effect of the polymer molecular weight on the nucleation rate is similar to that on the growth rate. These results argue that the polymer effect on crystallization rate is mainly kinetic—through its modification of molecular mobility. We shall return to this point in the Discussion.

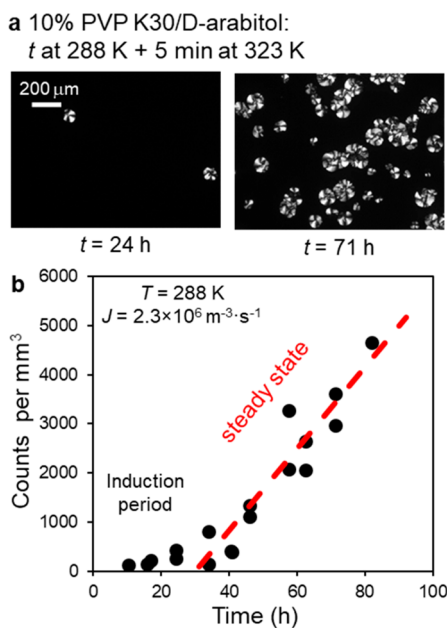
**D-Arabitol/PVP.** The same methods described above were applied to measure crystal nucleation rates in D-arabitol/PVP, with the exception that only one molecular-weight grade (K30) was used. Figures 6 and 7 show the typical data on this system; Table 3 collects the numerical results. As reported previously for pure D-arabitol,<sup>9</sup> two different polymorphs (I and II) can crystallize simultaneously, and this is also seen in the presence of PVP. The two polymorphs are distinguishable by their melting points (375 K for Form I, 355 K for Form II), by Raman spectroscopy, and by X-ray diffraction.<sup>9</sup> In this work, we focus on the faster-nucleating Form I and the effect of PVP on its nucleation.

Figure 6 illustrates how the one-stage method was used to measure the rate of nucleation in D-arabitol/PVP. As explained above, from the different sizes of the crystals (Figure 6a), their birth times are calculated using eq 1, and this yields a plot of





**Figure 6.** One-stage method for measuring crystal nucleation rates in D-arabitol/PVP K30. (a) A sample of D-arabitol containing 10 wt % PVP K30 after 2 days at 295 K. Two polymorphs can be observed (I and II). A range of crystal size is seen, from which the birth time of each crystal can be calculated (eq 1). (b) Density of crystal nuclei vs time. The slope of this plot in the steady state is the nucleation rate  $J$ .



**Figure 7.** Two-stage method for measuring nucleation rates in D-arabitol/PVP K30. (a) Crystals observed after a sample spent 24 or 71 h at 288 K followed by 5 h at 323 K. (b) Crystal density vs nucleation time at 288 K. The slope of this plot at the steady state is the nucleation rate  $J$ .

nuclei density versus time (Figure 6b). The slope of this plot at the steady state is the rate of nucleation  $J$ .

Figure 7 shows the typical data collected using the two-stage method for D-arabitol/PVP. This sample was nucleated at 288 K for different lengths of time, and the nuclei were allowed to

**Table 3.** Effects of PVP on the Rates of Nucleation and Growth in D-Arabitol<sup>a</sup>

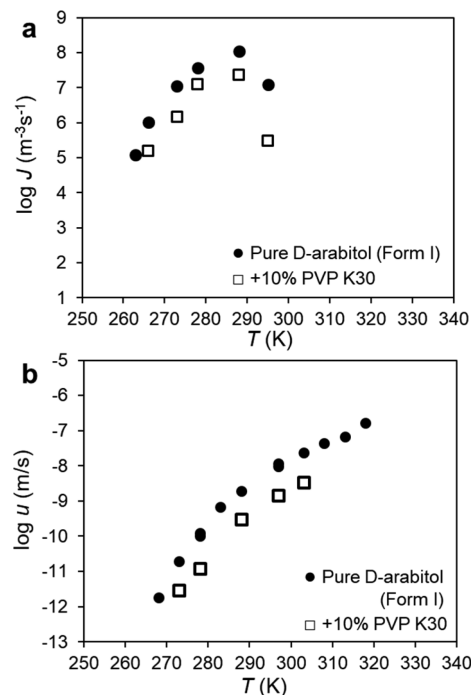
polymer (concentration)	$T$ (K)	$\log u$ (m/s)	$\log J$ (m <sup>-3</sup> s <sup>-1</sup> )	$\log J/u$ (m <sup>-4</sup> )
none (pure D-arabitol) <sup>b</sup>	263	-13.0	5.1	18.0
	266	-12.2	6.0	18.2
	273	-10.8	7.0	17.8
	278	-9.9	7.6	17.5
	288	-8.7	8.0	16.7
	295	-8.1	7.0	15.2
PVP K30 (5 wt %)	288	-9.3	7.6	16.8
PVP K30 (10 wt %)	266	-12.8 <sup>c</sup>	5.2	18.0
	273	-11.5	6.2	17.7
	278	-10.9	7.1	18.0
	288	-9.5	7.4	16.9
	295	-8.8	5.5	14.3
PVP K30 (15 wt %)	288	-9.8	6.8	16.6

<sup>a</sup>Notes: The error is  $\pm 0.2$  for each reported value of  $\log u$  or  $\log J$ .

<sup>b</sup>The  $\log u$  values for pure D-arabitol are obtained from a polynomial fit ( $n = 3$ ) of the data in Figure 8b. <sup>c</sup>Obtained by extrapolation of the data in Figure 8b to lower temperature.

grow at 323 K. A longer time at 288 K yielded more crystals observed at the growth temperature (Figure 7a), and from the increase of crystal density with nucleation time, we obtain the steady-state nucleation rate  $J$  (Figure 7b).

Figure 8a compares the rates of nucleation in pure D-arabitol<sup>9</sup> and D-arabitol containing 10 wt % PVP K30. In the

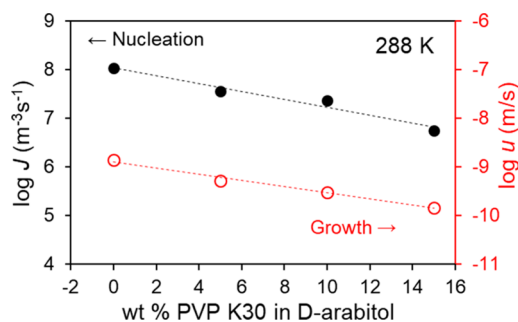


**Figure 8.** Effect of 10 wt % PVP K30 on the rate of nucleation (a) and growth (b) in D-arabitol.

temperature range investigated (near the temperature of the fastest nucleation in the pure liquid), PVP decreases the nucleation rate by approximately 10 times. A similar effect is seen on the rate of crystal growth in D-arabitol (Figure 8b), which is also reduced by the polymer by approximately a factor of 10 in the same temperature range. Thus, in both host

materials, D-sorbitol and D-arabitol, the polymer has similar effects on the rates of nucleation and growth, reducing both by a similar factor.

Figure 9 compares the effects of PVP concentration on the nucleation rate  $J$  and the growth rate  $u$  in D-arabitol at 288 K.



**Figure 9.** Effect of PVP concentration on the rates of crystal nucleation  $J$  and growth  $u$  in D-arabitol.

Both rates decrease with increasing polymer concentration, and the effects are approximately exponential [ $\log$  (rate) is approximately linear on polymer concentration]. As in the case of D-sorbitol (Figure 5), we observe a similar dependence of the nucleation rate and the growth rate in D-arabitol on PVP concentration.

**Homogeneous Nucleation.** For any nucleation process, a fundamental question is whether the process is homogeneous or heterogeneous. Homogeneous nucleation is stochastic, occurring in the volume of the material, whereas heterogeneous nucleation occurs at active sites catalyzed by foreign particles and interfaces. In this work, the nucleation process observed exhibits a steady state (Figures 2, 3, 6, and 7), and this is suggestive of homogeneous nucleation, for a heterogeneous process is expected to rapidly reach a saturation crystal density corresponding to the available active sites. To further evaluate the nature of the nucleation process, the thickness of the liquid films was varied, and the effect on the nucleation rate was evaluated. For a homogeneous process, the number of nuclei per unit volume should be independent of the film thickness, whereas for a heterogeneous process facilitated by the substrate, the apparent number of nuclei per unit volume should decrease with increasing film thickness. By this test, previous work reached the conclusion that nucleation in pure D-sorbitol and D-arabitol is homogeneous.<sup>9</sup> In this work, the test was repeated for polymer-doped materials and reached the same conclusion. For example, D-arabitol with 10 wt % PVP K30 was prepared at two thicknesses (10 and 140  $\mu\text{m}$ ). After crystallizing under the same condition (23 h at 288 K followed by 5 min at 323 K), the thicker sample showed 150 crystals per  $\text{mm}^3$  and the thinner sample 160 per  $\text{mm}^3$ . This shows that the observed nucleation process is a true volume process, unaffected by the presence of interfaces, as expected for homogeneous nucleation.

## DISCUSSION

This study has examined the effect of a polymer solute on crystal nucleation and growth in two glass-forming molecular liquids: D-sorbitol and D-arabitol. The PVP solute strongly inhibits nucleation and growth in the two systems, and under the conditions of this study, the effects are quite similar on the two processes. This similarity might come as a surprise given

the different kinetics of nucleation and growth. Here we discuss this result and argue that it arises from the similar kinetic barriers of the two processes.

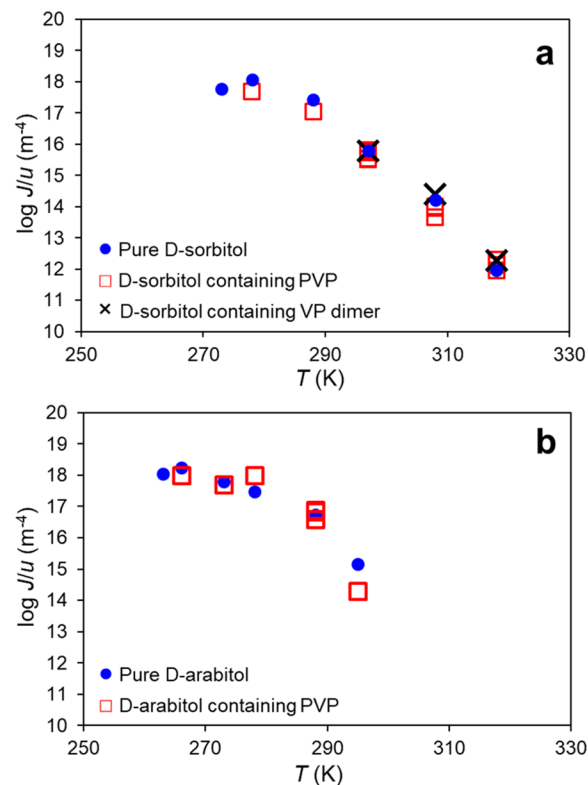
According to classical theories,<sup>8,23–26</sup> the rates of nucleation and growth in a pure liquid can be written as a product of thermodynamic and kinetic factors:

$$J = k_j F_j \quad (2)$$

$$u = k_u F_u \quad (3)$$

In these equations,  $k$  is a kinetic factor specifying the frequency at which attempts are made to grow a small nucleus ( $k_j$ ) or a macroscopic crystal ( $k_u$ ), and  $F$  is a thermodynamic factor appropriate for nucleation ( $F_j$ ) or growth ( $F_u$ ). For pure D-sorbitol and D-arabitol, previous work has shown that  $k_j$  and  $k_u$  have a similar temperature dependence<sup>5</sup> so that  $k_j/k_u$  is approximately constant. Under this assumption, the nucleation rates in the two liquids are well described by the classical nucleation theory (CNT) using reasonable nucleus/liquid interfacial energies.

The presence of a polymer solute alters both the kinetic factors and the thermodynamic factors for nucleation and growth. To evaluate these effects, we plot the ratio  $J/u$  as a function of temperature for the systems studied (Figure 10). Assuming nucleation and growth share a similar kinetic barrier,



**Figure 10.** Logarithm of the ratio  $J/u$  as a function of temperature for (a) D-sorbitol and (b) D-arabitol. Data are plotted for the pure liquids and the PVP-doped liquids. The open squares correspond to doped systems (see Tables 2 and 3) without distinguishing the polymer's molecular weights and concentrations. For D-sorbitol, the PVP used had different molecular weights (VP dimer, K12, K15, K30, and K90; see Table 1) and concentrations (0–10 wt %). For D-arabitol, the PVP used was PVP K30, and its concentration was 0–15 wt %. The collapse of data points indicates that under the conditions studied the polymer has similar effects on nucleation and growth.

this plot is expected to show a plateau at low temperatures at which both processes are limited by kinetics, as well as a decrease at high temperatures resulting from the larger thermodynamic barrier for nucleation than for growth. This pattern is indeed observed. Furthermore, the data points for the pure liquids (solid circles) coincide with those for PVP-doped liquids (open squares) within experimental error. This is a remarkable collapse of data points given the wide-ranging effects observed at different temperatures, different polymer concentrations, and in the case of D-sorbitol, different polymer molecular weights. Even the data on the VP dimer as dopant (crosses in Figure 10a) fall on the master curve for D-sorbitol.

We interpret the “master curve” behavior on the basis of eqs 2 and 3. According to these equations, the ratio  $J/u$  is given by

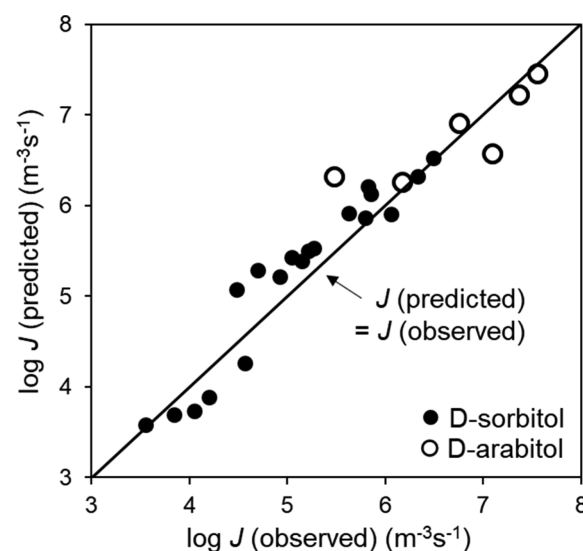
$$J/u = (k_j/k_u)(F_j/F_u) \quad (4)$$

Given the low polymer concentrations used (0–10 wt % in D-sorbitol and 0–15 wt % in D-arabitol), we expect a relatively small effect on the thermodynamic factors  $F_j$  and  $F_u$  and hence their ratio. This is supported by the small melting-point depression by the polymer ( $\sim 1$  K at 10 wt % PVP K30, see Figure S1 for the result on D-arabitol) relative to the much larger supercooling for our crystallization experiments (50 K on average for D-sorbitol; 90 K on average for D-arabitol). On the other hand, we expect a large decrease of the kinetic factors  $k_j$  and  $k_u$  by the polymer as a result of reduced molecular mobility. This is evident from the increase of the  $T_g$  of the host material by the polymer (Figure 1) and expected from the fact that low-concentration polymers can greatly increase viscosity<sup>27</sup> and reduce mobility.<sup>19</sup> Huang et al. showed that even at 1 wt %, a polymer can reduce crystal growth rate by a factor of 10, with the effect correlating with the polymer's segmental mobility.<sup>20</sup> Building on these observations, we explain the master curve behavior in Figure 10 as follows: Nucleation and growth share a similar kinetic barrier and involve similar molecular motions.<sup>9</sup> A polymer solute hinders these motions, slowing down both processes to a similar degree. As a result, the ratio  $J/u$  remains largely unchanged leading to the master curves.

In the development of amorphous formulations, the master curves in Figure 10 can be used to predict nucleation rates in a multicomponent system. If the rates of nucleation and growth,  $J_0$  and  $u_0$ , are known in a pure liquid at temperature  $T$ , the master curve behavior implies that the nucleation rate in a multicomponent system at the same temperature is given by

$$J = (J_0/u_0)u \quad (5)$$

where  $u$  is the rate of crystal growth in the multicomponent system at  $T$ . Since it is more time-consuming to measure nucleation rates than growth rates, this method provides a quick evaluation of the nucleation rate. Figure 11 presents a test of this method using data from the present study (Tables 2 and 3). Here the predicted  $J$  values using eq 5 are plotted against the observed values, and the diagonal line indicates perfect prediction. We note that all the points in Figure 11 cluster around the diagonal line. Together the observed nucleation rates cover 4 orders of magnitude, and the prediction can reproduce these rates without systematic error and with an average absolute error of 0.27 on the log scale, which is comparable to the experimental error.



**Figure 11.** Predicted vs observed nucleation rates in PVP-doped D-sorbitol and D-arabitol.

## CONCLUSION

We have measured the rates of crystal nucleation and growth in two glass-forming molecular liquids (D-sorbitol and in D-arabitol) in the presence of a dissolved polymer (PVP). At a relatively low concentration ( $\leq 15$  wt %), PVP can significantly slow down both nucleation and growth, with its effect increasing with concentration and molecular weight. Interestingly, the PVP effect on the nucleation rate is quite similar to that on the growth rate, so that their ratio is nearly a constant independent of polymer concentration and molecular weight. This supports the view that in these viscous liquids, nucleation and growth are both mobility-limited, and a dissolve polymer mainly functions as a mobility modifier, slowing the two processes by a similar factor. This result is relevant for the selection of polymers for stabilizing amorphous formulations and for the prediction of their performance. For example, our result indicates that the nucleation rate in a multicomponent system can be predicted from the rate of crystal growth and the crystallization kinetics of the pure system (Figure 11). This would avoid the laborious measurements of nucleation rates. The knowledge of both nucleation and growth rates will enable prediction of the overall rate of crystallization and the shelf life of multicomponent amorphous formulations. Further progress in this area will benefit from a broader test of the master curve behavior (Figure 10), including systems in which the second component is a high-mobility small molecule (e.g., surfactants commonly introduced in amorphous pharmaceutical formulations) and increases the rate of crystallization.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.cgd.9b01095>.

Figure S1. Effect of 10 wt % PVP K30 on the melting point of D-arabitol Form I. Figure S2. Effect of annealing on the glass transition temperature  $T_g$  of D-sorbitol containing 10 wt % PVP K30. Figure S3. The measurement for crystal growth rate in D-arabitol and D-arabitol containing 10% PVP K30 at 288 K (PDF)

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### Notes

AbbVie and University of Wisconsin-Madison jointly participated in study design, research, data collection, analysis and interpretation of data, writing, reviewing, and approving the publication. C.S. and G.Z. are employees of AbbVie and may own AbbVie stock.

The authors declare no competing financial interest.

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## DEDICATION

We dedicate this work to the memory of Joel Bernstein.

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